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FEB 18 1999

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Re: GONAL-F, follitropin alpha/beta

FDA Docket No. 98E-0488

Dear Mr. Wilson:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 5,156,957. The application was filed on November 28, 1997, under 35 U.S.C. § 156.

A copy of the application has been previously forwarded to the Food and Drug Administration (FDA) with a request for assistance. In reply, in a letter dated December 14, 1998, the FDA stated that the product had been subject to a regulatory review period before its commercial marketing, but that the approval was not the first permitted marketing or use of the product.

The term "drug product" is defined in 35 U.S.C. § 156(f)(2) as the active ingredient of "a new drug, antibiotic drug, or human biological product...as a single entity or in combination with another active ingredient."

The active ingredient in the approved product is follitropin alpha/beta (recombinant).[1] As noted in the above FDA letter, this product, follitropin alpha/beta, has been previously approved for commercial use or sale. The human drug products Humegon, Pregonal and Repronex all contain the active ingredient monotropins (which is naturally occurring and a combination of follicle simulating hormone (FSH) and luteinizing hormone (FH)).[2] FSH contains follitropin alpha/beta.[3] Humegon, Pregonal and Repronex were approved for commercial marketing on September 1, 1994, May 20, 1985, and January 30, 1997, respectively,[4] which was prior to the approval of the applicant's product, i.e., September 27, 1997. In addition, the human drug product Fertinex

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[1]The application for patent term extension incorrectly states that 37 CFR 1.740(a)(4) does not apply. The active ingredient, follitropin alpha/beta, has been previously approved as discussed in this letter.

[2]See the USP Dictionary of USAN and International Drug Names, 98, page 450.

[3]See the USP Dictionary of USAN and International Drug Names, 98, page 325.

[4]Approved Drug Products with Therapeutic Equivalence Evaluations, 18th Edition, 1998 (Orange Book), Prescription Drug Product List, page 3-209.

contains highly purified, naturally occurring FSH,[5] and was approved as early as September 18, 1986.[6] Recombinant follitropin alpha/beta is understood to have an amino acid sequence that is indistinguishable from natural follitropin alpha/beta.[7] Applying the definition of "product" provided in section 156(f) to the extension requirement of § 156(a)(5)(A), applicant's approval of GONAL-F does not qualify as the first permitted marketing or use of the product, since the recombinant form of follitropin alpha/beta is the same as the natural products that were previously approved.

However, 35 U.S.C. § 156(a)(5)(B) provides that:

> in the case of a patent which claims a method of manufacturing the product which primarily uses recombinant DNA technology in the manufacture of the product, the permission for the commercial marketing or use of the product after such regulatory period is the first permitted commercial marketing or use of a product manufactured under the process claimed in the patent;

U.S. Patent No. 5,156,957 claims a method of manufacturing a product, GONAL-F, which primarily uses recombinant DNA technology[8]. As a result, the '957 patent is eligible for extension if the approval of GONAL-F was the first permitted commercial marketing or use of a product manufactured using the recombinant DNA techniques claimed in the patent. Follitropin alpha/beta, as made by the process claimed in the patent, has not been shown to have been previously approved. The product FOLLISTIM™ (recombinant follitropin beta)(Organon) was

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[5]See the USP Dictionary of USAN and International Drug Names, 98, page 771.

[6]See Urofollitropin, Prescription Drug Product List, page 3-320.

[7]FDA regulations related to orphan drugs define two drugs as the same even if there are minor differences in the amino acid sequence. See 21 C.F.R. 316.3(b)(13)(ii)(A). But see Genentech, Inc. v. Bowen, 676 F. Supp. 301 (D.D.C. 1987). (A recombinant DNA-derived drug having the same amino acid sequence as the naturally occurring form is a different drug.)

[8] For example, claim 9 of U.S. Patent No. 5,156,957 states:

A method for producing the biologically active human fertility hormone FSH comprising culturing host mammalian cells in accordance with claim 1.

Claim 1 states:

A mammalian cell comprising a transformed cell transformed by at least a first expression vector, said transformed cell being capable of producing a biologically active heterodimeric human fertility hormone comprised of an alpha subunit and a beta subunit, each said subunit being encoded in nature by a distinct rRNA, said hormone being human FSH, the alpha subunit of said hormone being encoded by said first expression vector by which said transformed cell is also transformed, or progeny of said transformed cell containing the genetic information imparted by said vector or vectors.

also approved on September 29, 1997,[9] but this date is the same date, not before, the date of approval of GONAL-F. Thus, the contemporaneous approval of FOLLISTIM™, albeit a recombinant DNA product, does not preclude patent term extension based upon the regulatory review period of GONAL-F and the '957 patent is considered to be eligible for extension.

As a result, a determination by your office of the applicable regulatory review period is necessary. Notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Telephone inquiries regarding this matter should be directed to the undersigned at (703)306-3159.

Karin Tyson
Senior Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

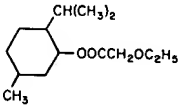
cc: Roger L. Browdy
Browdy and Neimark
419 Seventh Street NW
Suite 300
Washington DC 20004-2299

Attachments

[9]See the application for patent term extension of U.S. Patent No. 5,270,057; FOLLISTIM™, and "Two new fertility drugs offer convenient self-administration," Drug Topics, Oradell, November 3, 1997.

Footnote 2

Menglytate. $C_{14}H_{26}O_3$. 242.36. *p*-Menth-3-yl ethoxyacetate. *CAS-579-94-2.* INN.

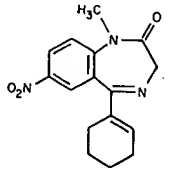


Menichlopholan — *See* Niclofolan.

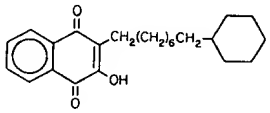
Meningococcal Polysaccharide Vaccine Group A. USP. *Immunizing agent (active).*

Meningococcal Polysaccharide Vaccine Group C. USP. *Immunizing agent (active).*

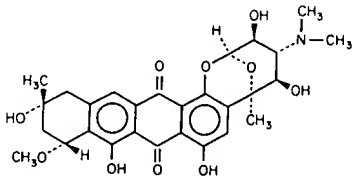
Menitrazepam. $C_{16}H_{17}N_3O_3$. 299.33. 5-(1-Cyclohexen-1-yl)-1,3-dihydro-1-methyl-7-nitro-2*H*-1,4-benzodiazepin-2-one. *CAS-28781-64-8.* INN; DCF. ✧*CB 4857*



Menoctone [*1967*] (me nok′ tone). $C_{24}H_{32}O_3$. 368.52. (1) 1,4-Naphthalenedione, 2-(8-cyclohexyloctyl)-3-hydroxy-; (2) 2-(8-Cyclohexyloctyl)-3-hydroxy-1,4-naphthoquinone. *CAS-14561-42-3.* INN. *Antimalarial.* (Sterling Winthrop†) ✧*Win 11,530; NSC-103336*



Menogaril [*1986*] (men′ oh ga ril). $C_{28}H_{31}NO_{10}$. 541.56. (1) 2,6-Epoxy-2*H*-naphthaceno[1,2-*b*]oxocin-9,16-dione, 4-(dimethylamino)-3,4,5,6,11,12,13,14-octahydro-3,5,8,10,13-pentahydroxy-11-methoxy-6,13-dimethyl-, [2*R*-(2α,3β,4α,5β,6α,11α,13α)]-; (2) (2*R*,3*S*,4*R*,5*R*,6*R*,11*R*,13*R*)-4-(Dimethylamino)-3,4,5,6,11,12,13,14-octahydro-3,5,8,10,13-pentahydroxy-11-methoxy-6,13-dimethyl-2,6-epoxy-2*H*-naphthaceno[1,2-*b*]oxocin-9,16-dione. *CAS-71628-96-1.* INN. *Antineoplastic.* ✧*U-52,047; NSC-269148*



Menotrophin (BAN) — *See* Menotropins.

Menotropins [*1967*] (men oh troe′ pins). **USP.** [Menotrophin is BAN.] An extract of human post-menopausal urine containing both follicle-stimulating hormone and luteinizing hormone. (1) Follicle stimulating hormone; (2) Follicle stimulating hormone. *CAS-9002-68-0. Gonad-stimulating principle.* Humegon (Organon); (Ortho Pharmaceutical†); Pergonal (Serono) *[Name previously used: Human Follicle Stimulating Hormone.]* ✧*FSH; HMG*

Menrium. Roche, Puerto Rico, brand of combination product; *See* Chlordiazepoxide; Estrogens, Esterified.

Menta-Bal. Marion Merrell Dow† brand of Mephobarbital.

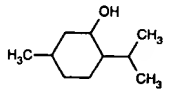
Mentane. Hoechst-Roussel† brand of Velnacrine Maleate.

Mentax. Penederm brand of Butenafine Hydrochloride.

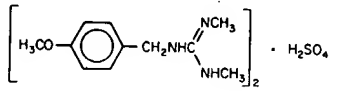
Mentha Oil. JAN.

l-Menthol (JAN) — *See* Levomenthol.

Menthol (men′ thole). **USP.** $C_{10}H_{20}O$. 156.27. [*dl*-Menthol is JAN.] Cyclohexanol, 5-methyl-2-(1-methylethyl)-. *CAS-1490-04-6. Antipruritic (topical).* Fisherman's Friend Lozenges (Bristol-Myers Products); Therapeutic Mineral Ice (Bristol-Myers Products); component of Dermoplast (Whitehall-Robins†); component of Minut-Rub (Bristol-Myers Products); component of Robitussin Cough Drops (Whitehall-Robins); component of Sarna (Stiefel); component of Theragesic (Mission Pharmacal)



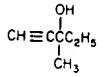
Meobentine Sulfate [*1977*] (may oh ben′ teen). $(C_{11}H_{17}N_3O)_2.H_2SO_4$. 512.63. [Meobentine is INN.] (1) Guanidine, *N*-[(4-methoxyphenyl)methyl]-*N′,N″*-dimethyl-, sulfate (2:1); (2) 1-(*p*-Methoxybenzyl)-2,3-dimethylguanidine sulfate (2:1). *CAS-58503-79-0; CAS-46464-11-3* [meobentine]. *Cardiac depressant (anti-arrhythmic).*



Mepacrine (INN, BAN) — *See* Quinacrine Hydrochloride.

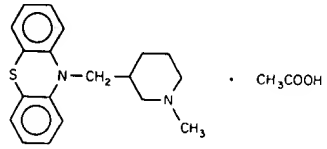
Mepadin. Marion Merrell Dow† brand of Meperidine Hydrochloride.

Meparfynol. $C_6H_{10}O$. 98.15. [Methylpentynol is INN and BAN.] 3-Methyl-1-pentyn-3-ol. *CAS-77-75-8.* MI. Dormison (Schering†)

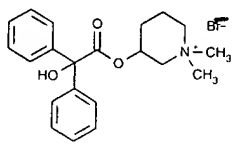


Mepartricin [*1975*] (me par′ tri sin). A methyl ester of partricin, which is a mixture in a constant ratio (about 1:1) of two polyene (heptaene) substances with very similar structure (not yet fully elucidated) and very similar biological properties. (1) Partricin, methyl-; (2) Methylpartricin. *CAS-11121-32-7.* INN; BAN. *Antifungal; antiprotozoal.* ✧*SPA-S-160; SN 654*

Mepazine Acetate. $C_{19}H_{22}N_2S.C_2H_4O_2$. 370.52. [Pecazine is INN and BAN.] 10-[(1-Methyl-3-piperidyl)methyl]phenothiazine. *CAS-24360-97-2; CAS-60-89-9* [mepazine]. NND 1964.



Mepenzolate Bromide (me pen′ zoe late). **USP.** $C_{21}H_{26}BrNO_3$. 420.35. (1) Piperidinium, 3-[(hydroxydiphenylacetyl)oxy]-1,1-dimethyl-, bromide; (2) 3-Hydroxy-1,1-dimethylpiperidinium bromide benzilate. *CAS-76-90-4; CAS-25990-43-6* [mepenzolate]. INN; BAN; JAN. *Anticholinergic.* Cantil (Merrell)



Foot note 3

Follicle Stimulating Hormone (BAN) — *See* Menotropins.

Follidrin — *See* Estradiol Benzoate.

Follitropin Alfa. $C_{437}H_{682}N_{122}O_{134}S_{13}$ (α-subunit). 10,205.88 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ (β-subunit). 12,485.34 (β-subunit). Follicle-stimulating hormone, glycoform α. [α-subunit]: Chorionic gonadotropin (human α-subunit protein moiety reduced); [β-subunit]: Follicle-stimulating hormone (human clone λ 15B β-subunit protein moiety reduced). *CAS-146479-72-3; CAS-56832-30-5* [α-subunit]; *CAS-110909-60-9* [β-subunit]. INN.

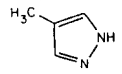
Follitropin Beta. $C_{437}H_{682}N_{122}O_{134}S_{13}$ (α-subunit). 10,205.88 (α-subunit); $C_{538}H_{833}N_{145}O_{171}S_{13}$ (β-subunit). 12,485.34 (β-subunit). Follicle-stimulating hormone, glycoform β. [α-subunit]: Chorionic gonadotropin (human α-subunit protein moiety reduced); [β-subunit]: Follicle-stimulating hormone (human β-subunit protein moiety reduced). *CAS-150490-84-9; CAS-56832-30-5* [α-subunit]; *CAS-110909-60-9* [β-subunit]. INN.

APDVQDCPEC	TLQENPFFSQ	PGAPILQCMG	CCFSRAYPTP
LRSKKTMLVQ	KNVTSESTCC	VAKSYNRVTV	MGGFKVENHT
ACHCSTCYYH	KS		
NSCELTNITI	AIEKEECRFC	ISINTTWCAG	YCYTRDLVYK
DPARPKIQKT	CTFKELVYET	VRVPGCAHHA	DSLYTYPVAT
QCHCGKCDSD	STDCTVRGLG	PSYCSFGEMK	E

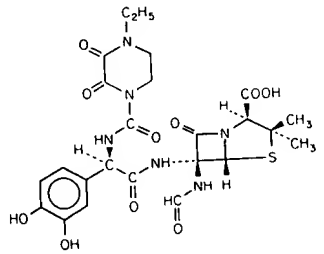
Follotropin — *See* Menotropins.

Follutein. Bristol-Myers Squibb† brand of Gonadotropin, Chorionic.

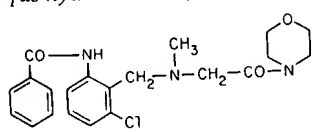
Fomepizole [*1990*] (foe me′ pi zole). $C_4H_6N_2$. 82.11. (1) 1*H*-Pyrazole, 4-methyl-; (2) 4-Methylpyrazole. *CAS-7554-65-6.* ✧*4-MP* INN. *Antidote* (*alcohol dehydrogenase inhibitor*).



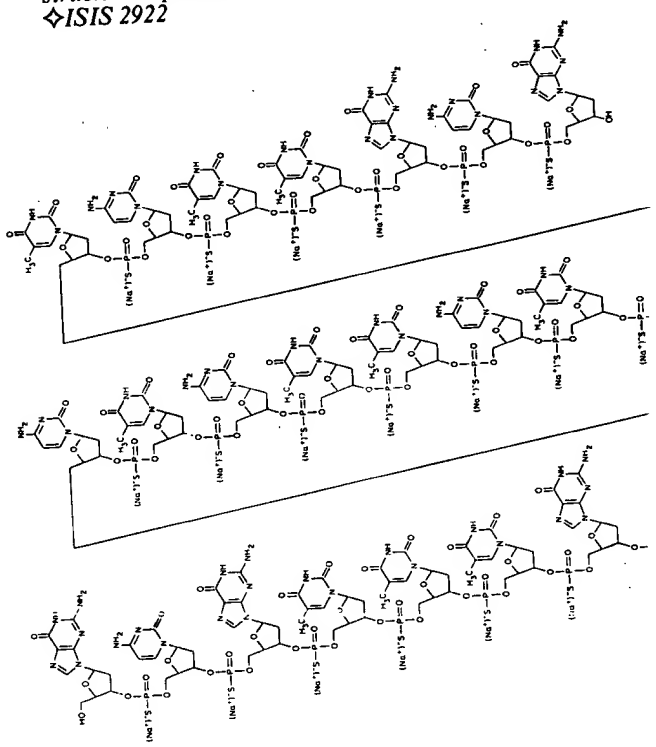
Fomidacillin. $C_{24}H_{28}N_6O_{10}S$. 592.59. (2*S*,5*R*,6*R*)-6-[(*R*)-2-(3,-4-Dihydroxyphenyl)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)acetamido]-6-formamido-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. *CAS-98048-07-8.* INN; BAN.



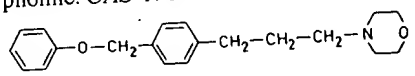
Fominoben. $C_{21}H_{24}ClN_3O_3$. 401.90. [Fominoben Hydrochloride is JAN.] 3′-Chloro-α-[methyl[(morpholinocarbonyl)-methyl]amino]-*o*-benzotoluidide. *CAS-18053-31-1.* INN; MI. ✧*PB 89 [as hydrochloride]*



Fomivirsen Sodium [*1996*] (foe mi′ vir sen). $C_{204}H_{243}N_{63}Na_{20}O_{114}P_{20}S_{20}$. 7122.16. [Fomivirsen is INN.] (1) Deoxyribonucleic acid d(*P*-thio)(G-C-G-T-T-T-G-C-T-C-T-T-C-T-T-C-T-T-G-C-G), eicosasodium salt; (2) 2′-Deoxy-*P*-thioguanylyl-(5′→3′)-2′-deoxy-*P*-thiocytidylyl-(5′→3′)-2′-deoxy-*P*-thioguanylyl-(5′→3′)-2′-deoxy-*P*-thiothymidylyl-(5′→3′)-2′-deoxy-*P*-thiothymidylyl-(5′→3′)-2′-deoxy-*P*-thioguanylyl-(5′→3′)-2′-deoxy-*P*-thiocytidylyl-(5′→3′)-2′-deoxy-*P*-thiothymidylyl-(5′→3′)-2′-deoxy-*P*-thiocytidylyl-(5′→3′)-2′-deoxy-*P*-thiothymidylyl-(5′→3′)-2′-deoxy-*P*-thiocytidylyl-(5′→3′)-2′-deoxy-*P*-thiothymidylyl-(5′→3′)-2′-deoxy-*P*-thiothymidylyl-(5′→3′)-2′-deoxy-*P*-thioguanylyl-(5′→3′)-2′-deoxy-*P*-thiocytidylyl-(5′→3′)-2′-deoxyguanosine, eicosasodium salt. *CAS-160369-77-7; CAS-144245-52-3* [fomivirsen]. *Antisense antiviral used in the therapy of cytomegalovirus retinitis.* (ISIS) *[Note—The following structure is positioned vertically due to space limitations.]* ✧*ISIS 2922*

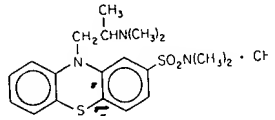


Fomocaine. $C_{20}H_{25}NO_2$. 311.43. 4-[3-(α-Phenoxy-*p*-tolyl)pr pyl]morpholine. *CAS-17692-39-6.* INN; BAN; MI.



Fonatol — *See* Diethylstilbestrol.

Fonazine Mesylate [*1967*] (foe′ na zeen). C 487.67. [Dimetotiazine is INN; Dimetotiaz JAN; Dimethothiazine is BAN.] (1) 10*H*-P sulfonamide, 10-[2-(dimethylamino)propyl] monomethanesulfonate; (2) 10-[2-(Dimeth *N,N*-dimethylphenothiazine-2-sulfonamide sulfonate. *CAS-7455-39-2; CAS-7456-24-otonin inhibitor.* ✧*IL-6302 mesylate; 85*



† Brand name formerly used, and/or firm no longer concerned with this product.

MEGESTROL ACETATE

TABLET; ORAL

	MEGESTROL ACETATE				
AB	ROXANE	40MG	N74458 002 SEP 29, 1995		

MELPHALAN

TABLET; ORAL

	ALKERAN				
+	GLAXO WELLCOME	2MG	N14691 002		

MELPHALAN HYDROCHLORIDE

INJECTABLE; INJECTION

	ALKERAN				
+	GLAXO WELLCOME	EQ 50MG BASE/VIAL	N20207 001 NOV 18, 1992		

MENOTROPINS (FSH;LH)

INJECTABLE; INJECTION

	HUMEGON				
AB	ORGANON	75 IU/VIAL;75 IU/VIAL	N20328 001 SEP 01, 1994		
AB		150 IU/VIAL;150 IU/VIAL	N20328 002 SEP 01, 1994		
	PERGONAL				
AB	+ SERONO	75 IU/AMP;75 IU/AMP	N17646 001		
AB	+	150 IU/AMP;150 IU/AMP	N17646 002 MAY 20, 1985		
	REPRONEX				
AB	FERRING	75 IU/VIAL;75 IU/VIAL	N73598 001 JAN 30, 1997		
AB		150 IU/VIAL;150 IU/VIAL	N73599 001 JAN 30, 1997		

MEPENZOLATE BROMIDE

TABLET; ORAL

	CANTIL				
+	HOECHST MARION RSSL	25MG	N10679 003		

MEPERIDINE HYDROCHLORIDE

INJECTABLE; INJECTION

	DEMEROL				
AP	+ SANOFI	25MG/ML	N05010 007		
AP	+	50MG/ML	N05010 002		
AP	+	75MG/ML	N05010 009		
AP	+	100MG/ML	N05010 003		
	MEPERIDINE HCL				
AP	+ ABBOTT	10MG/ML	N88432 001 AUG 16, 1984		
AP	ASTRA	10MG/ML	N81002 001 JUL 30, 1993		
AP		50MG/ML	N89784 001 MAR 31, 1989		
AP		100MG/ML	N89788 001 MAR 31, 1989		
AP	ELKINS SINN	25MG/ML	N80445 001		
AP		50MG/ML	N80445 002		
AP		75MG/ML	N80445 003		
AP		100MG/ML	N80445 004		
AP	INTL MEDICATION	10MG/ML	N81309 001 AUG 30, 1993		
AP	MALLINCKRODT	10MG/ML	N40163 001 MAY 12, 1997		
AP	STERIS	10MG/ML	N73443 001 MAR 17, 1992		
AP		50MG/ML	N73444 001 MAR 17, 1992		
AP		100MG/ML	N73445 001 MAR 17, 1992		
AP	WYETH AYERST	25MG/ML	N80455 007		
AP		50MG/ML	N80455 008		
AP		75MG/ML	N80455 009		
AP		100MG/ML	N80455 010		

SYRUP; ORAL

	DEMEROL				
AA	+ SANOFI	50MG/5ML	N05010 005		
	MEPERIDINE HCL				
AA	ROXANE	50MG/5ML	N88744 001 JAN 30, 1985		

TABLET; ORAL

	DEMEROL				
AA	+ SANOFI	50MG	N05010 001		
AA	+	100MG	N05010 004		
	MEPERIDINE HCL				
AA	BARR	50MG	N88639 001 JUL 02, 1984		

Footnote 4

Footnote 5

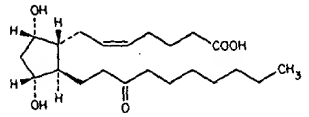
Unipres. Solvay Pharmaceuticals† brand of combination product; *See* Hydralazine Hydrochloride; Hydrochlorothiazide; Reserpine.

Unisom. Pfizer brand of Doxylamine Succinate.

Unitop [Veterinary]. Hoffmann-LaRoche† brand of Cuprimyxin.

Univasc. Schwarz Pharma brand of Moexipril Hydrochloride.

Unoprostone. $C_{22}H_{38}O_5$. 382.54. (+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoic acid. *CAS-120373-36-6*. INN.



UP 74. Code designation for Nixylic Acid.

UP 83. Code designation for Niflumic Acid.

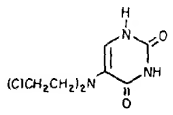
UP 106. Code designation for Propizepine.

UP 107. Code designation for Bepiastine.

UP 164. Code designation for Morniflumate.

Uracil. $C_4H_4N_2O_2$. 112.09. 2,4(1*H*,3*H*)-Pyrimidinedione. JAN.

Uracil Mustard [*1962*] (yoor' a sil). $C_8H_{11}Cl_2N_3O_2$. 252.10. [Uramustine is INN and BAN.] (1) 2,4(1*H*,3*H*)-Pyrimidinedione, 5-[bis(2-chloroethyl)amino]-; (2) 5-[Bis(2-chloroethyl)amino]uracil. *CAS-66-75-1*. USP XXII. *Antineoplastic.* ✧*U-8344; NSC-34462*

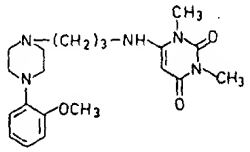


Uralenic Acid — *See* Enoxolone.

Uramustine (INN, BAN) — *See* Uracil Mustard.

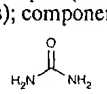
Uranin — *See* Fluorescein Sodium.

Urapidil. $C_{20}H_{29}N_5O_3$. 387.48. 6-[[3-[4-(*o*-Methoxyphenyl)-1-piperazinyl]propyl]amino]-1,3-dimethyluracil. *CAS-34661-75-1*. INN; BAN; JAN; MI.



Urbanyl. Hoechst-Roussel† brand of Clobazam.

Urea (yoor ee' a). USP. CH_4N_2O. 60.06. (1) Urea; (2) Carbamide. *CAS-57-13-6*. JAN. *Diuretic.* Nutraplus (Galderma); (Pfanstiehl); Ureaphil (Abbott); component of Aqua Care (Menley & James); component of Panafil (Rystan)

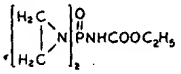


Ureaphil. Abbott brand of Urea.

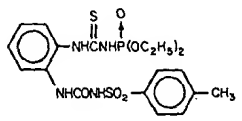
Urecholine. Merck brand of Bethanechol Chloride.

† Brand name formerly used, and/or firm no longer concerned with this product.

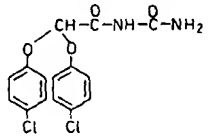
Uredepa [*1962*] (yoor e dee' pa). $C_7H_{14}N_3O_3P$. 219.18. (1) Carbamic acid, [bis(1-aziridinyl)phosphinyl]-, ethyl ester; (2) Ethyl [bis(1-aziridinyl)phosphinyl]carbamate. *CAS-302-49-8*. INN. *Antineoplastic.* ✧*AB-100; NSC-37095*



Uredofos [*1977*] (yoo re' doe fos). $C_{19}H_{25}N_4O_6PS_2$. 500.54. (1) Phosphoramidic acid, [[[2-[[[[(4-methylphenyl)sulfonyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-, diethyl ester; (2) Diethyl [thio[*o*-[3-(*p*-tolylsulfonyl)-ureido]phenyl]carbamoyl]phosphoramidate. *CAS-52406-01-6*. INN; BAN. *Anthelmintic (veterinary).* ✧*RH-32,565; RH-565*

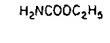


Urefibrate. $C_{15}H_{12}Cl_2N_2O_4$. 355.18. Glyoxyloylurea *aldehydo*-[bis(*p*-chlorophenyl)acetal]. *CAS-38647-79-9*. INN.



Urethan (NF XIII) — *See* Urethane.

Urethane. $C_3H_7NO_2$. 89.09. *CAS-51-79-6*. INN; BAN; DCF. *[Name previously used: Ethyl Carbamate.]* ✧*NSC-746*



Urex. 3M Pharmaceuticals brand of Methenamine Hippurate.

Urispas. SmithKline Beecham brand of Flavoxate Hydrochloride.

Uritone. Parke-Davis† brand of Methenamine.

Urocit-K. Mission Pharmacal brand of Potassium Citrate.

Urofollitropin [*1987*] (yoor oh fol li troe' pin): [Urofollitrophin is BAN.] A preparation of purified extract of human postmenopausal urine containing follicle-stimulating hormone (FSH). (1) Urofollitropin; (2) Urofollitropin. *CAS-97048-13-0*. INN. *Hormone (follicle-stimulating).* Fertinex (Serono); Metrodin (Serono)

Urogastrone. An inhibitory factor of gastric secretion derived from human urine. *CAS-9010-53-1*. JAN.

Urokinase [*1965*] (yoor oh kin' ace). A plasminogen activator isolated from human sources. (1) Kinase (enzyme-activating), uro-; (2) Urokinase. *CAS-9039-53-6*. INN; BAN; JAN. *Plasminogen activator.* Abbokinase (Abbott); Breokinase (Sterling Winthrop†); Win-Kinase (Sterling Winthrop†)

Urokon Sodium. Mallinckrodt† brand of Acetrizoate Sodium.

Uromiro. Bracco Industria Chimica S.p.A., Italy, brand of Iodamide.

Uromiron. Bracco Industria Chimica S.p.A., Italy, brand of Iodamide.

Uro-Phosphate. ECR brand of combination product; *See* Methenamine; Sodium Phosphate, Monobasic.

Urotropin. Parke-Davis† brand of Methenamine.

Ursodeoxycholic Acid (INN; BAN) — *See* Ursodiol.

TYROPANOATE SODIUM

CAPSULE; ORAL
BILOPAQUE
+ NYCOMED 750MG N13731 001

URACIL MUSTARD

CAPSULE; ORAL
URACIL MUSTARD
+ ROBERTS LABS 1MG N12892 001

UREA

INJECTABLE; INJECTION
UREAPHIL
+ ABBOTT 40GM/VIAL N12154 001

UREA; *MULTIPLE*
SEE HYDROCORTISONE ACETATE; UREA

UREA, C-13

POWDER FOR RECONSTITUTION; ORAL
MERETEK UBT KIT (W/ PRANACTIN)
+ MERETEK 125MG/VIAL N20586 001 SEP 17, 1996

UREA, C-14

CAPSULE; ORAL
PYTEST
+ TRI MED SPECLTS 1 uCi N20617 001 MAY 09, 1997

PYTEST KIT
+ TRI MED SPECLTS 1 uCi N20617 002 MAY 09, 1997

UROFOLLITROPIN

INJECTABLE; INTRAMUSCULAR
METRODIN
+ SERONO 75 IU/AMP N19415 002 SEP 18, 1986

UROFOLLITROPIN

INJECTABLE; INTRAMUSCULAR
METRODIN
+ SERONO 150 IU/AMP N19415 003 SEP 18, 1986

INJECTABLE; SUBCUTANEOUS
FERTINEX
+ SERONO 75 IU/AMP N19415 005 AUG 23, 1996

150 IU/AMP N19415 004 AUG 23, 1996

URSODIOL

CAPSULE; ORAL
ACTIGALL
+ NOVARTIS 300MG N19594 002 DEC 31, 1987

TABLET; ORAL
URSO
+ AXCAN 250MG N20675 001 DEC 10, 1997

VALACYCLOVIR HYDROCHLORIDE

TABLET; ORAL
VALTREX
+ GLAXO WELLCOME EQ 500MG BASE N20487 001 JUN 23, 1995

VALPROATE SODIUM

INJECTABLE; INJECTION
DEPACON
+ ABBOTT EQ 100MG BASE/ML N20593 001 DEC 30, 1996

VALPROIC ACID

CAPSULE; ORAL
DEPAKENE
AB + ABBOTT 250MG N18081 001

Footnote 6

Footnote 7

Subpart E—Open Protocols for Investigations

316.40 Treatment use of a designated orphan drug.

Subpart F—Availability of Information

316.50 Guidelines.
316.52 Availability for public disclosure of data and information in requests and applications.

AUTHORITY: 21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371.

SOURCE: 57 FR 62085, Dec. 29, 1992, unless otherwise noted.

Subpart A—General Provisions

§ 316.1 Scope of this part.

(a) This part implements sections 525, 526, 527, and 528 of the act and provides procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics. This part sets forth the procedures and requirements for:

(1) Submissions to FDA of:

(i) Requests for recommendations for investigations of drugs for rare diseases or conditions;

(ii) Requests for designation of a drug for a rare disease or condition; and

(iii) Requests for gaining exclusive approval for a drug product for a rare disease or condition.

(2) Allowing a sponsor to provide an investigational drug product under a treatment protocol to patients who need the drug for treatment of a rare disease or condition.

(b) This part does not apply to food, medical devices, or drugs for veterinary use.

(c) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 316.2 Purpose.

The purpose of this part is to establish standards and procedures for determining eligibility for the benefits provided for in section 2 of the Orphan Drug Act, including written recommendations for investigations of orphan drugs, a 7-year period of exclusive marketing, and treatment use of investigational orphan drugs. This part is also intended to satisfy Congress' requirements that FDA promulgate procedures for the implementation of sections 525(a) and 526(a) of the act.

§ 316.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act as amended by section 2 of the Orphan Drug Act (sections 525–528 (21 U.S.C. 360aa–360dd)).

(2) *Active moiety* means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

(3) *Clinically superior* means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug (that is otherwise the same drug) in one or more of the following ways:

(i) Greater effectiveness than an approved orphan drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or

(ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or

(iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

(4) *Director* means the Director of FDA's Office of Orphan Products Development.

(5) *FDA* means the Food and Drug Administration.

(6) *Holder* means the sponsor in whose name an orphan drug is designated and approved.

(7) *IND* means an investigational new drug application under part 312 of this chapter.

(8) *Manufacturer* means any person or agency engaged in the manufacture of a drug that is subject to investigation and approval under the act or the biologics provisions of the Public Health Service Act (42 U.S.C. 262–263).

(9) *Marketing application* means an application for approval of a new drug filed under section 505(b) of the act, a request for certification of an antibiotic under section 507 of the act, or an application for a biological product/establishment license submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

(10) *Orphan drug* means a drug intended for use in a rare disease or condition as defined in section 526 of the act.

(11) *Orphan-drug designation* means FDA's act of granting a request for designation under section 526 of the act.

(12) *Orphan-drug exclusive approval* or *exclusive approval* means that, effective on the date of FDA approval as stated in the approval letter of a marketing application for a sponsor of a designated orphan drug, no approval will be given to a subsequent sponsor of the same drug product for the same indication for 7 years, except as otherwise provided by law or in this part.

(13) *Same drug* means:

(i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.

(ii) If it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

(A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior.

(B) Two polysaccharide drugs would be considered the same if they had identical saccharide repeating units, even if the number of units were to vary and even if there were postpolymerization modifications, unless the subsequent drug could be shown to be clinically superior.

(C) Two polynucleotide drugs consisting of two or more distinct nucleotides would be considered the same if they had an identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars), unless the subsequent drug were shown to be clinically superior.

(D) Closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, would be considered the same unless the subsequent drug was shown to be clinically superior.

(14) *Sponsor* means the entity that assumes responsibility for a clinical or nonclinical investigation of a drug, including the responsibility for compliance with applicable provisions of the act and regulations. A sponsor may be an individual, partnership, corporation, or Government agency and may be a manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of drugs. For purposes of the Orphan Drug Act, FDA considers the real party or parties in interest to be a sponsor.

Footnote 7

*301 676 F.Supp. 301

GENENTECH, INC., et al., Plaintiffs,
v.
Otis R. BOWEN, et al., Defendants.

No. Civ. A. 87-605 SSH.
United States District Court,
District of Columbia.

Sept. 18, 1987.

Matter came before Court on motions of drug manufacturers seeking summary judgment in challenge to Food and Drug Administration's designation of human growth hormone drug as orphan drug. The District Court, Stanley S. Harris, J., held that designation of human growth hormone drug as "orphan drug" did not violate Orphan Drug Act or Food and Drug Administration's binding regulations implementing Act, despite contention that drug and pituitary-derived human growth hormone were same drug.

Ordered accordingly.

1. DRUGS AND NARCOTICS ⚿9
138 ----
138I Drugs and Druggists in General
138k2 Federal Regulation
138k9 New drugs.
D.D.C. 1987.
Nothing in Orphan Drug Act modifies manufacturer's ultimate responsibility to demonstrate that drug is both safe and effective. Federal Food, Drug, and Cosmetic Act, Secs. 505, 525-528, as amended, 21 U.S.C.A. Secs. 355, 360aa-360dd; Orphan Drug Act, Sec. 5, 21 U.S.C.A. Sec. 360ee.

2. DRUGS AND NARCOTICS ⚿9
138 ----
138I Drugs and Druggists in General
138k2 Federal Regulation
138k9 New drugs.
D.D.C. 1987.
While any number of drugs may receive development-phase benefits of Orphan Drug Act, only one manufacturer may receive exclusive marketing rights unless exclusive marketer consents in writing or is incapable of providing sufficient quantities of drug. Federal Food, Drug, and Cosmetic Act, Sec. 527(a, b), as amended, 21 U.S.C.A. Sec. 360cc(a, b).

3. ESTOPPEL ⚿68(2)
156 ----
156III Equitable Estoppel
156III(B) Grounds of Estoppel
156k68 Claim or Position in Judicial Proceedings
156k68(2) Claim inconsistent with previous claim or position in general.
D.D.C. 1987.
Drug company's original assertion challenging validity of human growth hormone's designation as orphan drug on ground that designated drug and drug manufactured by challenging company were "same drug" for purposes of Orphan Drug Act did not estop company from seeking to invalidate drug's designation as orphan drug on ground that drug and pituitary-derived human growth hormone were same drug. Federal Food, Drug, and Cosmetic Act, Secs. 525-528, as amended, 21 U.S.C.A. Secs. 360aa-360dd; Orphan Drug Act, Sec. 5, 21 U.S.C.A. Sec. 360ee.

4. FEDERAL CIVIL PROCEDURE ⚿312
170A ----
170AII Parties
170AII(H) Intervention
170AII(H)1 In General
170Ak312 Nature and purpose.
D.D.C. 1987.
Providing opportunity to litigate claims not adequately raised by parties is one purpose of intervention. Fed.Rules Civ.Proc.Rule 24, 28 U.S.C.A.

5. ADMINISTRATIVE LAW AND PROCEDURE ⚿704
15A ----
15AV Judicial Review of Administrative Decisions
15AV(B) Decisions and Acts Reviewable
15Ak704 Finality.

[See headnote text below]

5. DRUGS AND NARCOTICS ⚿10
138 ----
138I Drugs and Druggists in General
138k2 Federal Regulation
138k10 Administrative action and judicial review or enforcement.
D.D.C. 1987.

Challenges to Food and Drug Administration's designation of human growth hormone as orphan drug were ripe for review, notwithstanding fact that Food and Drug Administration had not rejected new drug application of challengers on basis of drug's orphan drug exclusivity; designation of drug as orphan drug was final and no longer subject of review at agency, challengers would be required to provide sufficient data to demonstrate clinical superiority of their drugs to obtain new drug application approval, and claims did not involve actual disputes but rather required court to construe meaning of statutory language and published Food and Drug Administration policy. Federal Food, Drug, and Cosmetic Act, Sec. 527(a, b), as amended, 21 U.S.C.A. Sec. 360cc(a, b).

6. ADMINISTRATIVE LAW AND PROCEDURE ⚷663
   15A ----
   15AV Judicial Review of Administrative Decisions
   15AV(A) In General
   15Ak663 Jurisdiction.

[See headnote text below]

6. DRUGS AND NARCOTICS ⚷10
   138 ----
   138I Drugs and Druggists in General
   138k2 Federal Regulation
   138k10 Administrative action and judicial review or enforcement.

D.D.C. 1987.

Provision of Food and Drug Act which vests federal Courts of Appeals with jurisdiction over appeals from orders refusing or withdrawing approval of new drug applications did not deprive district court of jurisdiction over competing drug manufacturers' challenge to Food and Drug Administration's designation of competitor's human growth hormone as orphan drug. Federal Food, Drug, and Cosmetic Act, Sec. 505(h), as amended, 21 U.S.C.A. Sec. 355(h).

7. DRUGS AND NARCOTICS ⚷9
   138 ----
   138I Drugs and Druggists in General
   138k2 Federal Regulation
   138k9 New drugs.

D.D.C. 1987.

Designation of human growth hormone drug as "orphan drug" did not violate Orphan Drug Act or Food and Drug Administration's binding regulations implementing Act, despite contention that drug and pituitary-derived human growth hormone were same drug; drug had synthetic origin and did not present danger of contamination with disease agent that was associated with human growth hormone obtained from human cadavers. Federal Food, Drug, and Cosmetic Act, Secs. 525-528, as amended, 21 U.S.C.A. Secs. 360aa-360dd; Orphan Drug Act, Sec. 5, 21 U.S.C.A. Sec. 360ee.

***302** James R. Phelps, Robert A. Dormer, Washington, D.C., Brian C. Cunningham, Patricia J. Kenney, South San Francisco, Cal., for plaintiff Genentech.

Nancy L. Buc, Salem M. Katsh, Washington, D.C., for plaintiff Nordisk.

Robert Poluska, Paul L. Perito, John P. Wintrol, Conan N. Louis, Washington, D.C., for plaintiff/intervenor.

Joel E. Hoffman, Washington, D.C., for Eli Lilly.

Jeffrey N. Gibbs, Washington, D.C., for Ares-Serono.

Jeffrey Hunter Moon, U.S. Atty's. Office, Washington, D.C., for Government.

Fletcher E. Campbell, Jr., Rockville, Md., for FDA.

MEMORANDUM OPINION

STANLEY S. HARRIS, District Judge.

This matter is before the Court on the separate, but similar, motions of plaintiff Genentech, Inc. (Genentech), intervenor-defendant Ares-Serono, Inc. (Serono), and intervenor-plaintiffs Nordisk Gentoffe A/S and Nordisk-U.S.A. (Nordisk) for partial summary judgment. In its complaint, Genentech, the manufacturer and marketer of a synthetic human growth hormone produced through recombinant DNA technology, alleges that the recent decision of the Food and Drug Administration (FDA), represented in this Court by defendants Otis R. Bowen, Secretary of Health and Human Services, and Frank E. Young, Commissioner of the Food and Drugs Administration, to approve a recombinant DNA human growth hormone product manufactured

by intervenor-defendant Eli Lilly and Company (Lilly) violated the Administrative Procedure Act, the Orphan Drug Act, and the Fifth Amendment to the United States Constitution. The pending motions challenge the validity of the FDA's designation, prior to marketing approval, of Lilly's drug as an orphan drug. Upon consideration of the motions, the oppositions thereto, and the entire record, the motions for partial summary judgment are denied.

Background

This case revolves around certain elements of the FDA's implementation of the Orphan Drug Act, Pub.L. No. 97-414, 96 Stat. 2049 (1983) (codified, as amended, at 21 U.S.C. Secs. 360aa-360ee). (FN1) Accordingly, it is appropriate to begin with a review of the history and purposes of the Orphan Drug Act, as well as the particular circumstances which gave rise to this lawsuit.

I. The Orphan Drug Act

As food and drug regulatory statues go, the Orphan Drug Act (the Act) is relatively straightforward and politically uncontroversial. A pharmaceutical company often must spend $80 million or more to develop a single new drug. 128 Cong.Rec. S15307 (daily ed. Dec. 16, 1982) (statement of Sen. Hawkins) (remarks inserted in record). When the potential market for a drug is small--because the number of persons afflicted with the particular disease or condition which the drug treats is relatively small--it may be impossible for the manufacturer to recover its sizable research and development investment, much less realize an acceptable return on that investment. Id. The Act is designed to combat the ***303** general unwillingness of pharmaceutical manufacturers to invest in the development of commercial drugs for the treatment of diseases which, although devastating to their victims, afflict too small a proportion of the population to make them commercially viable. Id. (FN2)

[1] The Act seeks to encourage the development of "orphan drugs" by reducing the overall financial cost of development, while enhancing the developer's ability to recover that cost through sale of the drug. Specifically, the Act attempts to reduce development costs by streamlining the FDA's approval process for orphan drugs, (FN3) by providing tax breaks for expenses related to orphan drug development, (FN4) by authorizing the FDA to assist in funding the clinical testing necessary for approval of an orphan drug, (FN5) and by creating an Orphan Products Board to coordinate public and private development efforts. (FN6) The Act seeks to enhance the orphan drug manufacturer's ability to recover his investment by granting the manufacturer seven years of exclusive marketing rights "for such drug for such [rare] disease or condition." (FN7) A "rare disease or condition" is one which "affects less than 200,000 persons in the United States," or one which "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." 21 U.S.C. Sec. 360bb(a)(2). (FN8)

Qualification for orphan drug benefits occurs in a two-step process. At any phase of the research and development process, a manufacturer who believes its drug will treat a "rare disease or condition" may apply to the FDA for designation as "a drug for a rare disease or condition" (i.e., an orphan drug). 21 U.S.C. Sec. 360bb. Orphan drug designation enables the manufacturer or sponsor to take advantage of the Act's tax benefits, to request pre-approval ***304** clinical testing recommendations, and to request financial assistance from the FDA in conducting the necessary clinical investigations. However, manufacturers receiving orphan drug designation must consent to limited public disclosure of the designation by the FDA, 21 U.S.C. Sec. 360bb(b), and may be asked by the FDA to include in the drug's clinical testing, under an "open protocol" method, persons presently suffering from the rare disease. 21 U.S.C. Sec. 360dd. Although the Act does not limit the number of drugs that may be designated for treatment of a particular rare disease, see 21 U.S.C. Sec. 360bb, the FDA's present policy is to not consider requests for orphan drug designation made after that drug has received full FDA marketing approval for that particular disease. See Policy of Eligibility of Drugs for Orphan Designation, 51 Fed.Reg. 4505, 4505 (1986).

[2] While any number of drugs may receive the development-phase benefits of the Act, only one manufacturer may receive exclusive marketing rights. This post-development benefit is reserved for the first manufacturer to receive full FDA approval of its drug as safe and effective for

commercial sale. The Act provides, in pertinent part:

> [I]f the [FDA] ... approves an application ... for a drug designated under section 360bb of this title for a rare disease or condition, the [FDA] may not approve another application ... for such drug for such disease or condition for a person who is not the holder of such approved application ... until the expiration of seven years from the date of approval of the approved application....

21 U.S.C. Sec. 360cc(a). (FN9) The FDA may authorize another manufacturer to produce "such drug for such disease or condition" only if the exclusive marketer consents in writing or is incapable of providing sufficient quantities of the drug. See supra note 7.

As originally enacted, the Act limited the availability of exclusive marketing rights to drugs "for which a United States Letter of Patent may not be issued...." See Pub.L. No. 97-414, Sec. 2(a), 96 Stat. 2049, 2050 (1983). In considering the proposed legislation, the House Committee on Energy and Commerce found that many potential orphan drugs are not patentable, and stated: "In order to provide some incentive for the development of these particular orphan drugs, the Committee's bill includes an exclusive marketing right for the sponsor of such a drug." H.R.Rep. 840, 97th Cong., 2d Sess. 11, reprinted in 1982 U.S. Code Cong. & Admin. News 3577, 3583; see also 128 Cong.Rec. S13224 (daily ed. Oct. 1, 1982) (statement of Sen. Kassebaum) (Act "attempts to address the problems created when a promising drug treatment is not patentable by providing a 7-year exclusive marketing right for the sponsor of the drug.") Thus, the exclusivity provision of the Act was designed to complement the patent laws, filling gaps which might leave orphan drug manufacturers unprotected.

In 1985, Congress amended the Act to delete the non-patentability criterion in the exclusivity provision. See Orphan Drug Amendments of 1985, Pub.L. No. 99-91, Sec. 2, 99 Stat. 387, 387. The most extensive discussion of the purposes of the Act's exclusivity provision appears in the report prepared by the House Committee on Energy and Commerce to accompany the 1985 amendments to the Act. H.R. Rep. 153, 99th Cong., 1st Sess., reprinted in 1985 U.S. Code Cong. & Admin. News 301. The Committee began by noting that in the two-and-one-half years since its passage, the Act had "stimulated substantial new commitments" to the development of orphan drugs. Id. at 2, 1985 U.S.Code Cong. & Admin.News at 301. In discussing exclusivity, the Committee stated: "The purpose of the seven year period is to allow the sponsor of the orphan drug to recoup ***305** the cost of development by capturing all revenues from the sale of the drug for the rare disease." Id. at 3, 1985 U.S.Code Cong. & Admin.News at 303.

The Committee's expectation when it drafted the original provision in 1983 had been that exclusivity "would be used primarily by orphan drugs that [could] not get product patents." Id. (FN10) However, experience under the Act demonstrated that reliance on the incentives of patent protection for all patentable orphan drugs would be insufficient. First, many patents expire before completion of the clinical testing necessary for FDA marketing approval. Id. (FN11) Second, in many cases the product patent on a drug is held by an individual or company other than the one that intends to test the drug for use against a rare disease, and prior academic publication in the area precludes issuance of a use patent. Id. Accordingly, the fact that a product patent has been issued does not always ensure that a manufacturer will have a sufficient incentive to apply for permission to market the drug as an orphan drug.

In expanding the exclusivity provision to cover both patented and unpatented orphan drugs, the Committee noted that the provision would only benefit the sponsors of drugs with less than seven years of product patent protection available, and explained the difference between exclusivity under the Act and traditional patent protection. First, traditional patents generally offer much broader protection than orphan drug exclusivity, which is limited to treatment of a particular disease. Id. at 5, 1985 U.S. Code Cong. & Admin. News at 305. Second, while the inviolability of a patent is limited only by the holder's ability to enforce his rights in court, orphan drug exclusivity exists only so long as the sponsor adequately supplies the market. Id.

The Committee expressed its desire that elimination of the patentability distinction, while probably still not making orphan drugs profitable business ventures, would strengthen development by providing greater certainty to potential orphan drug

sponsors.

> The Act and this bill do attempt to reduce the disincentives for their development and give drug company sponsors some certainty as to the drug approval process at FDA and the market conditions they will face upon approval. The Committee hopes and anticipates that the amendment ... will encourage the development of new orphan drugs for use in previously untreated rare diseases.

Id. at 6-7, 1985 U.S. Code Cong. & Admin. News at 306. In floor debates, the exclusivity amendment either went undiscussed or was referred to as merely an administrative correction. See 131 Cong.Rec. S7025 (daily ed. May 23, 1985) (statement of Sen. Hatch) (a "small change" to eliminate "administrative difficulty").

In summary, a review of the legislative history reveals bipartisan support for both the purpose of the Orphan Drug Act--the development of safe and effective drugs for persons suffering from diseases so rare that ordinary market forces would not promote development, and the means of achieving the Act's goal--the creation of ***306** an economic atmosphere that would lead pharmaceutical manufacturers to invest in developing those drugs.

II. Factual Background

Human growth hormone (hGH) is a protein naturally produced and secreted by the human pituitary gland. In some children, between 6,000 and 15,000 in the United States, the pituitary gland does not produce enough hGH, resulting in stunted growth. Since 1958, the condition had been treated by supplementing a patient's natural hGH with hGH derived from the pituitary glands of human cadavers. (FN12) However, in 1985, use of pituitary-derived hGH was effectively eliminated by the discovery that three hGH patients who had been treated with hGH provided by NHPP had developed Creutzfeldt-Jakob Disease, an extremely rare but fatal condition, apparently due to exposure to a pathogen transmitted by the pituitary-derived hGH. Although no cases of Creutzfeldt-Jakob Disease have ever been linked to hGH distributed by Serono or KabiVitrum, neither has distributed pituitary-derived hGH in the United States since 1985. (FN13)

On October 17, 1985, the FDA granted Genentech, a pharmaceutical developer that specializes in the use of biotechnology (popularly known as "gene splicing"), marketing approval for a human growth product known commercially as Protropin. Genentech's product differs from pituitary-derived hGH in two important respects. First, it is synthesized through a recombinant DNA process utilizing E. coli bacteria, rather than produced in a human gland. (FN14) Second, Genentech's r-hGH product includes an amino acid group not commonly found in pituitary-derived hGH. (FN15) In terms of chemical structure, Genentech's r-hGH has the same sequence of 191 amino acids found in hGH, with an additional methionine amino acid group attached to one end of the molecule. Because Genentech's drug apparently does not present the risk of Creutzfeldt-Jakob Disease associated with pituitary-derived hGH, its approval in 1985 filled an important health need. On December 12, 1985, the FDA designated Protropin as an orphan drug, thus granting Genentech marketing exclusivity, pursuant to 21 U.S.C. Sec. 360cc, until December 12, 1992. Genentech estimates that it invested approximately $45 million developing its r-hGH product.

On June 12, 1986, the FDA designated an r-hGH drug developed by intervenor-defendant Lilly as an orphan drug for the treatment of human growth hormone deficiency. Unlike Genentech's r-hGH product, the chemical structure of Lilly's product is identical to that of natural, pituitary-derived hGH; that is, Lilly's drug does not contain the additional methionyl group found in Protropin. (FN16) On October 15, 1986, ***307** Lilly submitted to the FDA a New Drug Application (NDA) for its r-hGH product, seeking permission to market the drug commercially.

On November 3, 1986, Genentech submitted a "citizen petition" to the FDA. In it, Genentech took the position that Lilly's drug was, for the purposes of the Orphan Drug Act, the same as Protropin and therefore ineligible for marketing approval until 1992. Genentech asked the FDA to implement procedures under which the manufacturer of an orphan drug with marketing exclusivity would receive notice of, and the opportunity to contest, another manufacturer's claim that its drug was "different" for the purposes of Orphan Drug Act protection. Genentech also requested an administrative stay of approval of any new r-hGH products until Genentech received the proposed procedural opportunities, as well as an opportunity to seek judicial relief.

When Genentech learned that the FDA was preparing to approve the NDA for Lilly's methionyl-free r-hGH product, known commercially as Humatrope, Genentech sought an emergency stay from the FDA. When that request was denied, Genentech filed suit in this Court on March 6, 1987, seeking temporary, preliminary, and permanent injunctive relief, in addition to a declaratory judgment that the FDA's application of the Orphan Drug Act violated Genentech's statutory and constitutional rights.

The Court denied the plaintiff's request for a temporary restraining order on March 6, 1987. (FN17) That same day, the FDA formally responded to Genentech's citizen petition, denying the requests for implementation of new procedures and for a stay. The FDA also informed Genentech and Serono by letters that their methionyl-free r-hGH products had been designated orphan drugs. (FN18) On March 8, the FDA approved Lilly's NDA for Humatrope, thereby authorizing Lilly to market the drug commercially and triggering the orphan drug exclusivity provision of 21 U.S.C. Sec. 360cc. (FN19) Genentech and Nordisk have submitted NDAs for methionyl-free r-hGH products, but the FDA has not yet ruled on either NDA.

Discussion

I. Issues of Procedure and Justiciability

In opposing the motions for partial summary judgment, Lilly raises several threshold arguments relating to procedure and justiciability, rather than the substantive merits of the underlying claims. The Court finds none of them dispositive.

A. Claims Within the Scope of the Litigation

[3] Lilly argues that Genentech is not entitled to summary judgment because its motion is based on a claim not found in the complaint. While Lilly concedes that count V of Genentech's complaint challenges the validity of Humatrope's designation as an orphan drug, it points out that the rationale advanced by Genentech for this argument *308 was that Humatrope and Protropin are the "same" drug for the purposes of the Orphan Drug Act, not that Humatrope and pituitary-derived hGH are the same drug. Consequently, Lilly argues that Genentech should now, as "a matter of basic fairness," be estopped from ever seeking to invalidate Humatrope's designation on the ground that Humatrope and pituitary-derived hGH are the same drug. The Court disagrees.

[4] Genentech bases its motion on information acquired through discovery (i.e., review of the administrative record relating to approval of the Humatrope NDA). That the basis for Genentech's claims would continue to evolve as relevant information was unearthed in discovery is plainly envisioned by the Federal Rules of Civil Procedure. As the Supreme Court stated in Conley v. Gibson, 355 U.S. 41, 78 S.Ct. 99, 2 L.Ed.2d 80 (1957):

> [T]he Federal Rules of Civil Procedure do not require a claimant to set out in detail the facts upon which he bases his claim. * * * Such simplified "notice pleading" is made possible by the liberal opportunity for discovery and the other pretrial procedures established by the Rules to disclose more precisely the basis of both claim and defense and to define more narrowly the disputed facts and issues. Following the simple guide of Rule 8(f) that "all pleadings shall be construed as to do substantial justice," we have no doubt that petitioners' complaint adequately set forth a claim and gave the respondents fair notice of its basis. The Federal Rules reject the approach that pleading is a game of skill in which one misstep by counsel may be decisive to the outcome and accept the principle that the purpose of pleading is to facilitate a proper decision on the merits.

Id. at 47-48, 78 S.Ct. at 103 (footnote omitted). Lilly makes no argument that it has been prejudiced in its ability to respond to Genentech's revised rationale for its claim that Humatrope's orphan drug designation was improper. Lilly requested--and was given--an enlargement of time to file its opposition to Genentech's motion for partial summary judgment. Accordingly, the Court can find no basis for frustrating Genentech's efforts to have the Court decide this case according to the facts as they are revealed in the administrative record. (FN20)

B. Ripeness

[5] Lilly also argues that the FDA's designation of Humatrope as an orphan drug is not yet ripe for judicial review because neither Genentech, Serono, nor Nordisk has experienced a negative impact by virtue of the designation. The assertion that Lilly's entitlement to the pre-approval benefits available

under the Act (such as a tax break for development expenses) presents no legally cognizable injury is not challenged. The parties disagree, however, on the implications of the FDA's approval of the Humatrope NDA and Lilly's consequent right to seven years of marketing exclusivity. Lilly argues that none of the moving parties will suffer a cognizable injury until the FDA rejects an NDA on the basis of Humatrope's orphan drug exclusivity (at this time, Genentech and Nordisk have NDAs for methionyl-free r-hGH pending before the FDA). Genentech, Nordisk, and Serono respond that the FDA's designation constitutes "final agency action" which has had significant financial effects on their day-to-day operations.

"The law of ripeness, once a tangle of special rules and legalistic distinctions, is ***309** now very much a matter of practical common sense." Continental Air Lines, Inc. v. CAB, 522 F.2d 107, 124 (D.C.Cir.1974); see also, e.g., Ciba-Geigy Corp. v. United States Environmental Protection Agency, 801 F.2d 430, 434 (D.C.Cir.1986) (determination turns on "pragmatic balancing" of interests, rather than "nice legal distinctions"). When, as here, the Court is asked to review an administrative decision, the analytical framework is provided by Abbott Laboratories v. Gardner, 387 U.S. 136, 87 S.Ct. 1507, 18 L.Ed.2d 681 (1967). In Abbott Laboratories, the Supreme Court prescribed two levels of inquiry: "the fitness of the issues for judicial decision and the hardship to the parties of withholding court consideration." 387 U.S. at 149, 87 S.Ct. at 1515; see also, e.g., Office of Communication of the United Church of Christ v. FCC, 826 F.2d 101, 104 (D.C.Cir.1987). Application of both the "fitness" standard and the "hardship" standard to the circumstances of this case indicates that movants' challenges to the Humatrope designation are indeed ripe for review.

The "fitness" determination calls on the Court to determine "whether the agency's position is merely tentative or, on the other hand, whether the agency views its deliberative process as sufficiently final to demand compliance with its announced position." Ciba-Geigy, 801 F.2d at 436. There is no question that the administrative decision at issue here--the FDA's designation of Humatrope as an orphan drug--is final and no longer a subject of review at the agency. In notifying Serono of the orphan drug designation of Serono's methionyl-free r-hGH product (known as Saizen), the FDA informed Serono that if an NDA for another natural sequence hGH drug was approved before an NDA for Saizen (as Humatrope subsequently was), Serono could overcome the exclusivity of that first-approved drug only by providing sufficient data to demonstrate the clinical superiority of Saizen. (FN21) Thus, Serono, in preparing an NDA for Saizen, must now comply with additional requirements imposed as a result of the Humatrope designation. Moreover, the FDA insists that the designation is proper and does not indicate that any additional review will occur at the agency level. "Where, as here, the agency has stated that the action in question governs and will continue to govern its decisions, such action must be viewed as final in our analysis of ripeness." Better Government Ass'n v. Department of State, 780 F.2d 86, 93 (D.C.Cir.1986) (emphasis in original) (footnotes omitted).

Another element of the "fitness" inquiry is a consideration of whether the issue in dispute is to be resolved as a matter of law, or whether the Court will be called on to resolve factual disputes properly left to the agency. Abbott Laboratories, 387 U.S. at 149, 87 S.Ct. at 1515-16; Alascom, Inc. v. FCC, 727 F.2d 1212, 1217 (D.C.Cir.1984). The claims at issue here do not involve factual disputes, but rather require the Court to construe the meaning of statutory language and published FDA policy. Accordingly, the Court finds the movants' challenge to Humatrope's orphan drug designation to be fit for judicial review.

In approaching the "hardship" inquiry, the Court must ask whether the agency's position has a " 'direct and immediate ... effect on the day-to-day business' of the complaining parties." F.T.C. v. Standard Oil Co., 449 U.S. 232, 239, 101 S.Ct. 488, 493, 66 L.Ed.2d 416 (1980) (quoting Abbott Laboratories, 387 U.S. at 152, 87 S.Ct. at 1517); see also United States v. Storer Broadcasting Co., 351 U.S. 192, 199-200, 76 S.Ct. 763, 768-69, 100 L.Ed. 1081 (1956); Ciba-Geigy, 801 F.2d at 436; Better Government Ass'n, 780 F.2d at 92. Movants present compelling evidence that the FDA's designation of Humatrope, coupled with the subsequent NDA approval, will have a significant impact on their day-to- ***310** day research and development efforts. It is undisputed that the costs of developing and gaining marketing approval for the sort of drugs involved here run into the tens of millions of dollars. If Humatrope's orphan drug designation and approval stand, 21 U.S.C. Sec.

360cc(a) will bar for seven years approval of drugs being developed by movants. Accordingly, they find themselves locked in a dilemma: either continue to pour funding into drugs which, regardless of their safety and efficacy, may be barred from the marketplace, or accept the FDA's designation of Humatrope, cut their losses, and forego what could be a successful legal challenge. Such dilemmas are indicative of ripe disputes. See, e.g., Abbott Laboratories, 387 U.S. at 152, 87 S.Ct. at 1517; National Latino Media Coalition v. FCC, 816 F.2d 785, 790 (D.C.Cir.1987). (FN22)

Lilly's contention that no hardship will attach to Humatrope's designation until another NDA is formally denied on that basis is without merit. As discussed above, the designation is presently having, and will continue to have, a concrete effect on movants' day-to-day structuring of their businesses. The case law plainly indicates that such agency decisions may be reviewable even though not yet officially enforced. See Alascom, 727 F.2d at 1217 ; Continental Air Lines, 522 F.2d at 124-25. Although Lilly makes much of the fact that Serono has not yet submitted an NDA for Saizen, it is undisputed that the FDA has notified Serono that a Saizen NDA must be accompanied by data demonstrating clinical superiority over Humatrope, a costly and possibly unsustainable burden that is directly attributable to the challenged Humatrope designation. This imposition of additional responsibilities amply demonstrates the tangible impact of FDA's decision on Serono. See Ciba-Geigy, 801 F.2d at 436. Accordingly, the Court finds that both prongs of the Abbott Laboratories ripeness standard are satisfied with respect to the Humatrope orphan drug designation.

The Court reaches a different conclusion with respect to Serono's challenge to the orphan drug designation of Genentech's methionyl r-hGH Protropin. Although the Court's "fitness" discussion with respect to the Humatrope designation is equally applicable to the Protropin designation, no party has demonstrated any harm flowing from the Protropin designation. Unlike the Humatrope designation, which negatively affects the efforts of Genentech, Serono, and Nordisk to gain marketing approval for their methionyl-free r-hGH drugs, the Protropin designation (construed by the FDA to bar approval only of other methionyl r-hGH drugs) is not affecting the development efforts of any of the parties because Serono, Nordisk, and Lilly are not seeking to market methionyl r-hGH. (FN23) Accordingly, the Court finds that the "hardship" prong of the Abbott Laboratories test is not satisfied with respect to the Protropin designation. (FN24) Of course, the situation would be different if the FDA were to adopt, either on its own volition or as a result of this litigation, Genentech's position that Protropin's orphan drug exclusivity extends to methionyl-free r-hGH products.

*311 C. Subject Matter Jurisdiction

[6] In an extension of its argument that movants may only challenge the Humatrope designation if, and when, their NDAs are denied by the FDA, Lilly argues that this Court lacks subject matter jurisdiction over movants' challenges. Lilly relies on 21 U.S.C. Sec. 355(h), which vests the federal courts of appeals with jurisdiction over appeals "from an order of the Secretary refusing or withdrawing approval of [a new drug] application under this section." However, as explained above, the Court finds that movants have standing to challenge the Humatrope designation prior to a ruling on their NDAs. The Supreme Court has recognized that manufacturers without NDAs pending may be sufficiently affected by FDA decisions regarding the "new drug" status of a product to support a district court action under the Administrative Procedure Act, though not an appeal to the court of appeals. See Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 627, 93 S.Ct. 2469, 2482, 37 L.Ed.2d 207 (1973).

Moreover, it is unlikely that a court of appeals would have jurisdiction under 21 U.S.C. Sec. 355 (h) to review the validity of the Humatrope designation. Subsection (d) of 21 U.S.C. Sec. 355 enumerates seven grounds for denying a new drug application, and subsection (h) limits the courts of appeals' direct review jurisdiction to denials "under this subsection." A denial based on Humatrope's orphan drug exclusivity would be based on 21 U.S.C. Sec. 360cc(a) (which is silent on the matter of judicial review), not on a ground enumerated in 21 U.S.C. Sec. 355(d). Given the courts' narrow construction of jurisdiction under 21 U.S.C. Sec. 355(h), see Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 651, 93 S.Ct. 2488, 2493, 37 L.Ed.2d 235 (1973); Cutler v. Hayes, 818 F.2d 879, 887 n. 61 (D.C.Cir.1987), it is likely that movants would be rebuffed if they attempted to challenge the Humatrope designation in a court of

appeals. "Agency action taken under sections [of the Food, Drug, and Cosmetic Act] silent [on judicial review] are directly reviewable in a district court under some appropriate head of its jurisdiction, for courts of appeals have only such jurisdiction as Congress has chosen to confer upon them." Cutler, 818 F.2d at 887 n. 61. Accordingly, the Court holds that it has jurisdiction to entertain movants' challenge to the Humatrope designation.

II. Validity of the Humatrope Designation

[7] Movants contend that Humatrope's orphan drug designation violated both the Orphan Drug Act and the FDA's binding regulations implementing the Act. Their argument is based on the contention that Humatrope and pituitary-derived hGH are the same drug. In light of the peculiar facts of this case, the Court cannot accept movants' contention, and therefore must uphold the Humatrope designation.

The dispute presented here involves the proper application of 21 U.S.C. Sec. 360bb(a), the section of the Act governing orphan drug designations, which provides, in relevant part:

> (1) The manufacturer or the sponsor of a drug may request the Secretary to designate the drug as a drug for a rare disease or condition. If the Secretary finds that a drug for which a request is submitted under this subsection is being or will be investigated for a rare disease or condition and--
>
> (A) if an application for such drug is approved under section 355 of this title,
>
> * * *
> * * *
>
> the approval ... would be for use of such disease or condition, the Secretary shall designate the drug as a drug for such disease or condition.

Movants read this section as requiring that the orphan drug designation of a particular drug occur prior to approval of an NDA for that drug. They then argue that the approval of NDAs for pituitary-derived hGH in the 1970's precluded the orphan drug designation of Humatrope in 1986. Assuming, without deciding, that movants' construction of Sec. 360bb(a) is correct, the Court rejects their argument in this case because it is plain that Humatrope and pituitary-derived ***312** hGH are not the same drug for the purposes of Sec. 360bb(a).

A review of the Act's legislative history, as all of the parties would agree, sheds no direct light on the question of how broadly or narrowly the word "drug" should be construed in Sec. 360bb(a). The relevant committee reports and floor debates reveal broad, bipartisan support for the noble goal of providing treatment for the presently untreated, but do not evidence any focused consideration of important, but politically tiresome, details like the issue presented here. Instead, Congress directed that the FDA "shall by regulation promulgate procedures for the implementation" of Sec. 360bb(a). Unfortunately, the FDA has not, in the four years since passage of the Act, proposed any regulations defining "drug" for the purposes of Sec. 360bb(a). Thus, the Court--lacking either a legislative or administrative pronouncement--is left to apply the Act's broad policy objectives to the unique situation at hand. E.g., Chapman v. Houston Welfare Rights Organization, 441 U.S. 600, 608, 99 S.Ct. 1905, 1911, 60 L.Ed.2d 508 (1979); Automotive Parts Rebuilders Ass'n v. EPA, 720 F.2d 142, 159 n. 66 (D.C.Cir.1983).

Two related aspects of this particular case convince the Court that if Congress had been presented with the facts of this case, it would have considered Humatrope and pituitary-derived hGH different drugs for the purposes of Sec. 360bb(a). First, Humatrope, by virtue of its synthetic origin, does not present the danger of contamination with the Creutzfeldt-Jakob prion that is associated with hGH obtained from human cadavers. While movants are correct in noting that none of the reported cases of Creutzfeldt-Jakob Disease has been linked to hGH marketed under the approved NDAs held by Serono and Kabi, it is also true that so little is known about the contamination process that no manufacturer can warrant that its product is free from contamination. Thus, any pituitary-derived hGH product presents a risk (albeit unquantifiable) of lethal side effects not associated with r-hGH products such as Protropin and Humatrope. (FN25)

Second, the industry's response to the linking of Creutzfeldt-Jakob Disease to pituitary-derived hGh--withdrawal from the United States market--meant that regardless of the status of the Serono and Kabi NDAs, methionyl-free hGh would not be available to hGH-deficient children in this country. The

legislative history is replete with references to the fundamental need to provide treatment for presently untreated patients; the fact that NDAs for pituitary-derived hGh were technically still valid would not have convinced Congress that growth hormone deficiency was not a condition in need of new treatments. One need only imagine a world without methionyl r-hGH (plaintiff's Protropin) to appreciate the unacceptable ramifications of movants' argument when applied to this case. Without Protropin, children in need of supplemental hGH would go without treatment, while movants offered assurances that no additional orphan drug designations were necessary because valid, but unused, NDAs remained in effect. In enacting the Orphan Drug Act, Congress clearly focused on the availability of treatments, not the existence of prior NDAs. See, e.g., 131 Cong.Rec. S6243 (daily ed. May 15, 1985) (statement of Sen. Kennedy) (referring to need for orphan drugs to be "commercially available"); 128 Cong.Rec. S15307 (daily ed. Dec. 16, 1982) (statement of Sen. Hawkins) (same); cf. 21 U.S.C. Sec. 360cc(b)(1) (FDA may approve additional NDAs if holder of exclusive marketing rights is unable to supply the entire market). The Court is satisfied that Congress would have considered Humatrope sufficiently "different" to justify orphan drug designation. (FN26) *313. 6]

Nor did the Humatrope designation violate published FDA policy. Movants contend that under the FDA's "Policy of Eligibility of Drugs for Orphan Designation," published in the Federal Register on February 5, 1986, the FDA could not grant an orphan drug designation to Humatrope because the designation was submitted after the FDA had approved an NDA for "that drug" (i.e., pituitary-derived hGH). Notwithstanding the FDA's argument that its policy was designed to apply only to situations in which a sponsor attempted to secure orphan drug benefits after, rather than before, approval of that product for marketing, and the deference due an agency's interpretation of its own regulations, Udall v. Tallman, 380 U.S. 1, 16-17, 85 S.Ct. 792, 801, 13 L.Ed.2d 616 (1965), movants' argument must be rejected because the Court has concluded that Humatrope and pituitary-derived hGH are not the same drug.

Conclusion

In finding that Humatrope and pituitary-derived hGH are different drugs for the purposes of orphan drug designation under 21 U.S.C. Sec. 360bb, and that therefore the Humatrope designation is valid, the Court's holding is narrow and confined to the particular facts of this case. The Court expresses no opinion on the still-pending issue of whether Protropin's orphan drug exclusivity barred approval of Humatrope, and, in particular, sets down no universal rule for determining whether two drugs are "different" for the purposes of the Orphan Drug Act. That responsibility is statutorily imposed on the FDA. Until the FDA endeavors to meet that obligation, the courts will be forced to make case-by-case determinations based on the broad policies embodied in the Act. An appropriate Order accompanies this Memorandum Opinion.

ORDER

This matter is before the Court on the motions for partial summary judgment of plaintiff Genentech, Inc., intervenor-defendant Ares-Serono, Inc., and intervenor-plaintiffs Nordisk Gentoffe A/S and Nordisk-U.S.A. For the reasons set forth in the accompanying Memorandum Opinion, upon consideration of the motions, the oppositions thereto, and the entire record it hereby is

ORDERED, that the motions for partial summary judgment are denied. It hereby further is

ORDERED, that plaintiff Genentech, Inc.'s pending motion for a preliminary injunction is denied without prejudice.

SO ORDERED.

FN1. The Orphan Drug Act amends the Federal Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified, as amended, as 21 U.S.C. Chap. 9).

FN2. See also, e.g., Orphan Drug Act, Pub.L. No. 97-414, Sec. 1(b)(4)-(5), 96 Stat. 2049, 2049 (1983) (Congress' findings); H.R.Rep. No. 840, 97th Cong., 1st Sess. 1, reprinted in 1982 U.S. Code Cong. & Admin. News 3577, 3577; 128 Cong.Rec. S15307 (daily ed. Dec. 16, 1982) (statement of Sen. Kennedy) (remarks inserted in record); 128 Cong.Rec. H9678 (daily ed. Dec. 14, 1982) (statement of Rep. Weiss) (remarks inserted in record); id. at H9674 (statement of Rep. Waxman); 128 Cong.Rec. S13226-27 (daily ed. Oct. 1, 1982) (statement of Sen. Nunn); id. at S13224 (statement of Sen. Kassebaum); id. at

S13222-23 (statement of Sen. Hatch); 128 Cong.Rec. H7650 (daily ed. Sept. 28, 1982) (statement of Rep. Goodling).

FN3. See 21 U.S.C. Sec. 360aa(a) (orphan drug manufacturer may request from the FDA written recommendations for clinical and non-clinical tests necessary for approval). Nothing in the Act, however, modifies the manufacturer's ultimate responsibility, under 21 U.S.C. Sec. 355, to demonstrate that the drug is both safe and effective. See 128 Cong.Rec. H7650 (daily ed. Sept. 28, 1982) (statement of Rep. Ratchford) (remarks inserted in record).

FN4. See 26 U.S.C. Secs. 44H, 280C.

FN5. See 21 U.S.C. Sec. 360ee(a) ($4 million is available for each of the fiscal years 1986, 1987, and 1988).

FN6. See 42 U.S.C. Sec. 236.

FN7. See 21 U.S.C. Sec. 360cc(a). Marketing rights may be awarded to another manufacturer if the exclusive marketer consents in writing, or if, after providing the exclusive marketer with notice and an opportunity to submit its views, the FDA determines that the exclusive marketer is incapable of fully supplying the market. 21 U.S.C. Sec. 360cc(b).

*313_ FN8. As originally enacted, the Act required a showing of financial infeasibility before orphan drug benefits were made available, regardless of the size of the potential patient population. See Pub.L. No. 97-414, Sec. 2(a), 96 Stat. 2049, 2050 (1983). However, in 1984, Congress amended the Act to include the present presumption that all diseases afflicting fewer than 200,000 people in the United States require the benefits of orphan drug classification. See Health Promotion and Disease Prevention Amendments of 1984, Pub.L. No. 98-551, Sec. 4, 98 Stat. 2815, 2817. In doing so, Congress accepted the arguments of the FDA and the Department of the Treasury that the cost incurred in making such a showing was, in itself, a significant disincentive to seeking orphan drug benefits for drugs related to diseases affecting less than 200,000 persons, over the arguments of the Office of Management and Budget that such a rule would enable manufacturers to reap benefits for drugs that could be developed profitably without them. See 130 Cong.Rec. S14253-54, S14255 (daily ed. Oct. 11, 1984) (statement of Sen. Hatch); id. at S14255 (statement of Sen. Kassebaum).

FN9. Exclusivity is also available for antibiotic drugs which receive FDA certification under 21 U.S.C. Sec. 357, and biological products for which a license is issued under 42 U.S.C. Sec. 262 . See 21 U.S.C. Sec. 360bb(a)(2), (3). For the purposes of this case, only the application of the Act to drugs receiving approval through the "new drug" application process of 21 U.S.C. Sec. 355 is relevant.

FN10. Many drugs, once approved for sale, are ineligible for patent protection because to receive a patent an applicant must demonstrate that the invention is neither known nor obvious to others. The active ingredient of a drug may be patentable under either a "product patent" or a "use patent." "As a general rule, if the active ingredient in a drug exists in nature or is not sufficiently different from other existing active ingredients that it is known or obvious, then it cannot be the subject of a product patent. As a general rule, if the use of an active ingredient in a particular disease is obvious or is known because of literature published before a patent application is submitted to the Patent Office, then it cannot be the subject of a use patent." H.R.Rep. 153, 99th Cong., 1st Sess. 3 n. 1, reprinted in 1985 U.S. Code Cong. & Admin. News 301, 302.

FN11. Prior to the 1985 amendments, the FDA already had taken steps to address this problem by interpreting the Act to permit marketing exclusivity when the orphan drug's product patent had expired by the time the FDA approved the drug for commercial sale. However when a short period of patent protection remained, the FDA was placed in the unacceptable position of delaying approval until the patent expired. H.R.Rep. 153, 99th Cong., 1st Sess. 4, reprinted in 1985 U.S. Code Cong. & Admin. News 301, 304.

FN12. In 1963, the National Institutes of Health's National Hormone and Pituitary Program (NHPP) began distributing pituitary-derived hGH to patients in the United States, under an investigational new drug exemption. In 1979, intervenor-defendant Serono and KabiVitrum each acquired marketing rights for pituitary-derived hGH under approved

New Drug Applications (NDAs) and began distributing hGH in the United States.

FN13. Although Serono's and KabiVitrum's NDAs were not cancelled by the FDA pursuant to 21 U.S.C. Sec. 355(e), it is not clear to the Court whether those companies' withdrawals were purely voluntary, or whether there was a degree of informal compulsion exerted by the FDA. It is undisputed, however, that the withdrawals were occasioned by the linking of Creutzfeldt-Jakob Disease to pituitary-derived hGH, and that they effectively eliminated the supply of supplemental hGH in this country.

FN14. DNA stands for deoxyribonucleic acid. For a brief explanation of the recombinant DNA process, see Note, The Rutabaga That Ate Pittsburgh: Federal Regulation of Free Release Biotechnology, 72 Va.L.Rev. 1529, 1531-33 (1986). For a more detailed explanation, see Grobstein, The Recombinant-DNA Debate, Sci.Am., July 1977, at 22-29.

FN15. Large proteins, such as human growth hormone, are known as polypeptides, and consist of chains of different amino acid groups linked end to end. The sequence of the amino acids making up the chain distinguishes one type of protein from another.

*313 FN16. Genentech, Serono, intervenor-plaintiff Nordisk, and at least one other manufacturer also have developed methionyl-free r-hGH products. Requests for orphan drug designation were submitted by Genentech, Serono, and Nordisk to the FDA during 1986.

FN17. At the TRO hearing on March 6, a hearing on plaintiff's motion for a preliminary injunction was scheduled for March 26, 1987. Opposition briefs for intervenor-defendants Lilly and Serono were filed on March 20, and for the federal defendants on March 24. On March 24, Genentech moved to extend the date for filing its reply brief, as well as the date for hearing argument on the preliminary injunction motion, indefinitely while plaintiff studied the administrative record filed by the FDA. The Court granted that motion on March 25. Considering the length of time that has passed, and the volume of water that has passed under the proverbial bridge since plaintiff's motion for a preliminary injunction was placed in judicial suspended animation, the Court has concluded that the pending preliminary injunction motion should be denied without prejudice to plaintiff's right to seek such relief in the future. This will allow plaintiff to argue any legal theory supported in the record, without being confined by the standards applicable to reply memoranda, and will ensure that the defendants have an adequate opportunity to respond to plaintiff's arguments.

FN18. In response to the FDA's approval of the Humatrope NDA, Genentech amended its complaint to reflect the changed factual circumstances. All references in this opinion are to the amended complaint.

FN19. The FDA has requested additional information from Nordisk regarding its request for orphan drug designation. Consequently, the FDA has not yet issued a final decision on Nordisk's request.

FN20. Similarly, the Court rejects Lilly's argument that intervenors Serono and Nordisk may not challenge Humatrope's designation on the ground that Humatrope is the same as pituitary-derived hGH. Not only is the claim within the scope of the litigation, but there is no basis for Lilly's argument that the intervenors may not raise claims not raised by Genentech. Indeed, providing an opportunity to litigate claims not adequately raised by the parties is one of the purposes of intervention. See Fed.R.Civ.P. 24; see also, e.g., Stewart-Warner Corp. v. Westinghouse Electric Corp., 325 F.2d 822, 827 (2d Cir.1963) ("The whole tenor and framework of the Rules of Civil Procedure preclude application of a standard which strictly limits the intervenor to those defenses and counterclaims which the original defendant could himself have interposed"). Moreover, Lilly was presented with opportunities to challenge the scope of both Nordisk's complaint and Serono's cross-claim and failed to object.

FN21. On the same day, March 6, 1987, the FDA sent a similar letter to Genentech, notifying plaintiff that its methionyl-free r-hGH drug (Protropin II) had been designated an orphan drug. However, for no apparent reason, the letter to Genentech did not state, as did the letter to Serono, that Genentech could overcome the exclusivity of an earlier-approved drug by demonstrating clinical

superiority. That opportunity was extended to Genentech on July 10, 1987, in a letter from the FDA's Director of the Office of Orphan Products Development.

FN22. While the mere possibility of financial losses may not be sufficient to establish "hardship," when compliance with the agency's decision is certain to impose costs that would not be incurred if litigation were successful, financial impact is sufficient. Abbott Laboratories, 387 U.S. at 153-54, 87 S.Ct. at 1518; Ciba-Geigy, 801 F.2d at 438-39.

FN23. In a reversal of position, Lilly, after arguing early in its opposition brief that the Humatrope designation was not yet ripe for review, joins Serono's motion to invalidate the Protropin designation at the end of the same brief. Lilly makes no effort to harmonize its conflicting positions on this aspect of the ripeness issue.

FN24. Although the parties generally have addressed the justiciability issue in terms of the ripeness doctrine, this case appears to present, as the FDA seems to suggest, a situation where the issue is equally amenable to characterization as a standing problem. The choice of terms has no substantive effect because the Court would find that Serono, Nordisk, and Lilly lack standing to challenge the Protropin designation inasmuch as none has suffered a legally cognizable injury "fairly traceable" to the designation which is "likely to be redressed" through invalidation. Allen v. Wright, 468 U.S. 737, 751, 104 S.Ct. 3315, 3324, 82 L.Ed.2d 556 (1984).

*313_ FN25. Movants place great emphasis on statements made by Lilly and by the FDA officials describing the common chemical characteristics of pituitary-derived hGH and methionyl-free r-hGH. It is clear from the record that the close similarity of the two drugs allowed the FDA to focus its evaluation of the Humatrope NDA. Nevertheless, the Court does not read the FDA's comments to indicate that the two drugs were identical in every relevant respect. Lilly's apparent concession in its answer that "all methionyl-free growth hormone products are the same drug" is not relevant to the legal basis for a decision made not by Lilly, but rather by the FDA.

FN26. The court also rejects two arguments advanced by movants which, if adopted, would represent amendment of the Orphan Drug Act through judicial fiat. First, movants contend that designation of Humatrope violates the spirit of the Act by granting orphan drug benefits to a profitable drug. This possibility was explicitly considered--and accepted--in 1984 when the definition of rare disease or condition was amended to include all diseases afflicting fewer than 200,000 people in the United States. See supra note 8. This Court does not sit to judge the wisdom of that policy choice. Second, movants argue that the Humatrope designation violates the spirit of the Act by granting benefits to a manufacturer that did not rely on the Act's incentives when deciding whether to invest in new drug development. Consequently, movants assert that Congress did not intend for Lilly to profit from orphan drug designation. To accept movants' argument, however, would be to write into the Act an effective date that Congress chose not to impose; Congress chose to make orphan drug benefits available immediately. The Court declines movants' invitation to impose an additional condition on the receipt of benefits under the Act.

Footnote 9

HELP ?

Two new fertility drugs offer convenient self-administration

Drug Topics; Oradell; Nov 3, 1997; Norma Beavers;

Volume: 141
Issue: 21
Start Page: 30-32
ISSN: 00126616
Subject Terms: Product introduction
Fertility
Prescription drugs
Classification Codes: **8641**: *Pharmaceuticals industry*
7500: *Product planning & development*
9190: *US*
Geographic Names: US
Companies: Organon Inc
Serono Laboratories Inc

Abstract:

*Two new fertility drugs - Gonal-F (**follitropin** alfa for injection), from Serono Laboratories and Follistim (**follitropin** beta for injection), from Organon Inc. - appear ready to decrease the long-time shortage of fertility treatments. The drugs are strikingly similar and received Food & Drug Administration marketing clearance recently. Both drugs are non-urine-based recombinant follicle-stimulating hormones indicated for ovulation induction as well as for use in assisted reproductive technologies, such as in vitro fertilization. Their main selling point seems to be that both **follitropin** alfa and **follitropin** beta offer a higher degree of purity and consistency associated with genetically engineered products. Both can be self-administered by patients and are therefore more convenient to use than older-generation urine based fertility drugs.*

Full Text:

Two new fertility drugs-Gonal-F (follitropin alfa for injection), from Serono Laboratories, and Follistim (follitropin beta for injection), from Organon Inc.-appear ready to decrease the long-time shortage of fertility treatments. The drugs are strikingly similar and received Food & Drug Administration marketing clearance on Sept. 29.

Both drugs are non-urine-based recombinant follicle-stimulating hormones indicated for ovulation induction as well as for use in assisted reproductive technologies, such as in vitro fertilization. Their main selling point seems to be that both follitropin alfa and follitropin beta offer a higher degree of purity and consistency associated with genetically engineered products. Both can also be self-administered by patients and are therefore more convenient to use than older-generation urine-based fertility drugs. The urine-based preparations require the aid of a healthcare provider or the patient's partner to inject them deep into muscle tissue, according to Serono and Organon.

Serono is playing up follitropin alfa as a product that "offers women the convenience of subcutaneous self-administration and the high degree of purity and consistency inherent in a recombinant product." Meanwhile, Organon is promoting follitropin beta as "the first recombinant fertility drug that can be self-administered, enabling patients to treat themselves at home."

Historically, infertility drugs have been produced by extracting fertility hormones, or gonadotropins, from the urine of postmenopausal women. This labor-intensive process requires daily collection of the raw material from women donors, and, given natural fluctuations in urine composition, the manufacturing process is often difficult and complicated. Scott Chappel, Ph.D., Serono's executive v.p. of science and technology, said, "The use of recombinant technology eliminates these issues and delivers a consistent product, free of urinary substances."

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 14 1998

Re: Gonal-F
Docket No. 98E-0488

Stephen G. Kunin
Deputy Assistant Commissioner for
Patent Policy and Projects
U.S. Patent and Trademark Office
Box Pat. Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Mr. Kunin:

This is in regard to the application for patent term extension for U.S. Patent No. 5,156,957 filed by Genzyme Corporation under 35 U.S.C. § 156. The human drug product claimed by the patent is Gonal-F (follitropin alpha/beta), which was assigned New Drug Application (NDA) No. 20-378.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it does not represent the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in Glaxo Operations UK Ltd. v. Quigg, 706 F. Supp. 1224 (E.D. Va. 1989), aff'd, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on September 29, 1997, which makes the submission of the patent term extension application on November 28, 1997, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the Federal Register, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs

cc: Roger L. Browdy
BROWDY AND NIEMARK
Suite 300
419 Seventh Street, N.W.
Washington, DC 20004-2299

JAN 12 1998

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Dear Mr. Wilson:

The attached application for patent term extension of U.S. Patent No. 5,156,957 was filed on November 28, 1997, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, GONAL-F, follitropin alpha/beta, has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156. However, the product FOLLISTIM™ (follitropin beta) was also approved on September 29, 1997 and an application for patent term extension based upon the regulatory review period of FOLLISTIM™ has been filed (U.S. Patent No. 5,270,057). If the regulatory review period for FOLLISTIM™ is the same as that of GONAL-F, then only one patent will be eligible for patent term extension.

Inquiries regarding this communication should be directed to the undersigned at (703) 306-3159 (telephone) or (703)308-6916 (facsimile).

Karin Tyson
Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

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